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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/656,935	BLUSZTAJN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11,12,14 and 18-21* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11,12,14,18 and 21* is/are rejected.

7)☒ Claim(s) *9,11,12,14,18 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/03 and 04/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed April 9, 2004 (hereinafter referred to as "the response") has been entered. Claims 9, 11,12, and 14 have been amended. Claims 7 and 17 have been cancelled. Claims 18-21 have been newly added.

Accordingly, Claims 9, 11, 12, 14, and 18-21 are pending in the instant application.

Newly submitted Claims 19 and 20 are directed to an invention that is independent and distinct from the elected invention for the following reasons:

The newly submitted claims are directed to a method for preventing brain function loss and/or memory loss in a patient. The elected invention is directed to a method for *in vivo* differentiation or *in vivo* upregulation of particular genes, namely choline acetyltransferase and vesicular acetylcholine transporter. The newly submitted claims would fall into a separate group, as they require prevention of specific clinical symptoms and therefore would require consideration of issues separate from those required for claims directed to treating patients with degenerating neurons. The methods are distinct because they cover the use of different patient populations and require different effects. Thus, the searches required for the two groups are not coextensive. Because the searches are not coextensive and because the issues involved are substantially different, a search and examination of both inventions in one application would constitute a serious burden on the Examiner.

Accordingly, Claims 19 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Amended Claims 9, 11, 12, and 14 and newly added Claims 18 and 21 are directed to an invention that is independent and distinct from the invention originally claimed for the following reasons:

The originally filed claims were directed to the *in vivo* administration of BMP-9 protein, whereas the amended claims and newly added claims now encompass the *in vivo* administration of a nucleic acid encoding BMP-9. The amended claims now recite "administering BMP-9." When given its broadest reasonable interpretation "administering BMP-9" includes administering BMP-9 by administering the nucleic acid encoding BMP-9. The originally filed claims did not include claims directed to the *in vivo* administration of a nucleic acid encoding BMP-9.

Since Applicant has received an action on the merits for the originally presented invention, this invention has bee constructively elected by original presentation for prosecution on the merits.

Accordingly, Claims 9, 11, 12, 14, 18, and 21 are examined herein only insofar as they encompass the *in vivo* administration of BMP-9 protein, the originally presented invention.

Claim Objections

Claims 9, 11, 12, 14, 18, and 21 are objected to because they encompass subject matter that goes beyond the scope of the elected invention, for the reasons discussed herein above. Applicants are required to amend the claims so that they no longer read on non-elected subject matter.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 9, 2004 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 11, 12, and 14 stand rejected and Claims 18 and 21 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 3-5 of the Office Action mailed 10/3/02, on pages 2-5 of the Office Action mailed 3/11/03, in the Advisory Action mailed 10/29/03, and for further reasons as discussed herein, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 4, paragraph 3 of the response, Applicants provide a misquote of the Examiner's comments. For the record, the correct quote is "[w]ith regard to Claims 11 and 12, Applicants assert that BMP-9 induced upregulation of the genes associated with the cholinergic phenotype would necessarily translate into a prediction that BMP-9 would upregulate thes genes in adult mouse and human tissue. However, no support is offered for this assertion." (pp. 2-3 of the Advisory Action mailed 10/29/03). Applicants go on to suggest that prior art (Walton et al. and Jonhagen et al.) and post-filing art (Tuszynski; Klein et al.; Nabeshima et al.; Wang et al.; and Liu et al.) relating to neurotrophic factors other than BMP-9 provide support for the claimed invention. The Examiner does not agree. The varied activities of NGF, GDNF, BMP-6, and BMP-7 are not sufficient to enable the instant invention, which is directed to treating a patient with degenerating neurons by the *in vivo* administration of BMP-9 protein.. The specification asserts that the utility of the instant invention is to produce a therapeutic effect in a patient. (see the specification at p. 2, lines 11-21). Applicants' arguments, however, are not commensurate in scope with the scope of the claims. For reasons of record, production of a therapeutic effect in a patient with AD, ALS, or another disease is highly unpredictable. The instant claims cover a wide variety of effects, including increased levels of choline acetyltransferase (ChAT) in the absence of a

therapeutic effect and increased levels of vesicular acetylcholine transporter (VAChT) in the absence of a therapeutic effect. However, these are not patentable utilities of the claimed invention. The only utility asserted in the specificaton consistent with the patent statute is to use the claimed method to produce a therapeutic effect. However, the specification does not teach the skilled artisan how to use any of the claimed methods to produce a therapeutic effect. For reasons of record and further for the reasons set forth below, the effect of BMP-9 within the brain of a diseased animal, with an ongoing pathological process, is unpredictable. The examples of the specification are limited to analysis of embryos. However, patients with AD are adults, not embryos. None of the examples of the specification constitute working examples of the claimed invention. Given the unpredictability in the art, the specification must provide specific guidance for producing a treatment effect in a patient, the sole utility set forth in the specification.

At page 5, paragraph 1 of the response, Applicants argue that one skilled in the art would reasonably expect the function of a neurotrophic factor in a **model system** to correlate with a similar function in the brain or nervous system of a patient (emphasis added). However, as noted above, the instant specification does not provide examples that use a model system. Normal mouse embryos do not constitute a model system for Alzheimer's disease. While animal models for Alzheimer's disease do exist, none were used here. See the detailed discussion at pages 2-5 of the Office Action mailed 10/3/03.

At page 6, paragraph 4 of the response, Applicants argue that "[w]hen BMP-9 is administered to the brain of a patient, it will increase the expression of neurotransmitters like choline acetyltransferase and vesicular acetylcholine transporter. This upregulation will at least partially replace the lost production of these same neurotransmitters caused by a degeneration of cholinergic neurons." For the record, choline acetyltransferase is not a neurotransmitter, but rather is an enzyme involved in the production of acetylcholine, which is a neurotransmitter. Likewise, vesicular acetylcholine transporter is not a neurotransmitter, but rather is a protein molecule involved in the transport of acetylcholine.

Applicants go on to argue that "it is not necessary for BMP-9 to actually replace neural connections, but only to replace the lost production of neurotransmitters." However, there is no evidence in either the prior art or the instant specification that increasing the production of acetylcholine in the brain (or more broadly "the nervous system" as recited in the claims) of patients with AD correlates with a treatment effect. Applicants' arguments are not commensurate in scope with the scope of the claims.

In the abstract titled "Bone morphogenetic protein-9 modulates acetylcholine content and choline acetyltransferase and vesicular acetylcholine transporter gene expression in the SN56 murine septal cell line," Lopez-Coviella et al. (1998; cited in IDS filed 4/9/04 with this response) discloses that

> "Incubation of SN56 cells with BMP-9 (10 ng/ml) for varying periods of time caused initial increases in ACh content (by 45% and 60% after 12 and 24 h, respectively). However, by 48 h BMP-9 caused a reduction in the cellular ACh content (by 40%) which remained stable for up to 72 h (figure 1). Consistent with this time-course, in cells treated for 48 h with varying concentrations of BMP-9, ACh content declined by as much as 60% in a concentration-dependent, saturable fashion with an EC50 for BMP-9 of 1.3 ng/ml.
>
> "Messenger RNA levels for ChAT and VAChT were reduced by 41% and 50%, respectively, 48 h after treatment with BMP-9. No significant changes were observed in the mRNA levels for these two cholinergic markers following shorter incubation periods with BMP-9 (i.e., at 12 and 24 h).

Thus, it is evident from the disclosure of Lopez-Coviella that BMP-9 down-regulates choline acetyltransferase (ChAT) and vesicular acetylcholine transporter (VAChT) gene expression. In fact, the reference states that the reduction in ACh content following exposure to BMP-9 "may be a consequence of down-regulation of VAChT and ChAT gene expression, since our results also show reduced levels of the mRNAs coding these two proteins." Thus, the evidence of record, as a whole, suggests that *in vivo* administration of BMP-9 protein in a patient is unpredictable, and is as likely to down-regulate expression of VAChT and ChAT as it is to up-regulate their expression.

At page 7, paragraph 2 of the response, Applicants assert that Claim 9 has been cancelled. On the contrary, Claim 9 remains pending. Applicants further assert that the claims have been amended so that they now recite the use of BMP-9 to treat patients by increasing the levels of choline acetyltransferase and vesicular acetylcholine transporter in patients with degenerating or malfunctioning neurons. However, for

the reasons discussed above, increasing enzyme and transporter levels in the nervous system of a patient in the absence of production of a concomitant therapeutic effect, lacks patentable utility. Since the specification asserts that a therapeutic effect will be achieved by application of the claimed method, it is the role of the specification to teach how to use the claimed method to achieve a therapeutic effect, the only utility asserted in the specification for *in vivo* administration of BMP-9 protein.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the patient populations to be "treated" and the wide variety of effects that fall within the scope of the claims, and the unpredictability for achieving a therapeutic effect upon the administration of BMP-9 protein, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention in a patient for therapeutic benefit.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 14, 18, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 stands rejected as indefinite in its recitation of "[a] method for treating a patient with degenerating cholinergic neurons" because no treatment effect is achieved. The claim concludes by reciting increased levels of choline acetyltransferase in the nervous system of the patient. Thus, the preamble of the claim is in conflict with the body of the claim.

At page 8, paragraph 2 of the response, Applicants assert that Claim 9 has been cancelled. On the contrary, Claim 9 remains pending.

Claim 14 is indefinite in its recitation of "[a] method for treating a patient with degenerating motor neurons" because no treatment effect is achieved. The claim concludes by reciting increased levels of choline acetyltransferase in the nervous system of the patient. Thus, the preamble of the claim is in conflict with the body of the claim. This is a new grounds of rejection necessitated by Applicants' amendment.

Claim 18 is indefinite in its recitation of "[a] method for treating a patient with degenerating cholinergic neurons" because no treatment effect is achieved. The claim concludes by reciting an increase in the level of vesicular acetylcholine transporter in the nervous system of the patient. Thus, the preamble of the claim is in conflict with the body of the claim. This is a new grounds of rejection necessitated by Applicants' amendment.

Claim 21 is indefinite in its recitation of "[a] method for treating a patient with degenerating motor neurons" because no treatment effect is achieved. The claim concludes by reciting increased levels of vesicular acetylcholine transporter in the nervous system of the patient. Thus, the preamble of the claim is in conflict with the body of the claim. This is a new grounds of rejection necessitated by Applicants' amendment.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Dianiece Jacobs, whose telephone number is (571) 272-0532.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER